REMARKS

Pursuant to a telephone interview with the Examiner on July 22, 2003, Applicants have amended claims 97 and 99 to more clearly define the subject matter claimed. Support for these amendments can be found throughout the specification.

Applicants are aware that there is a previously issued Restriction Requirement in the instant application. Applicants have expressed, in the previous response, the desire to shift election to Group II claims (97 and 99, and their dependent claims), and have canceled the Group I independent claim 91. In addition, in response to the initial Restriction Requirement, Applicants have elected, for search purposes only, polypeptide B (a polypeptide having the amino acid sequence of the C-terminal seven-cysteine skeleton on human OP-1) with traverse. As a result of this shift of election, and the amendment to the pending claims, Applicants hereby elect, for search purpose only, "a conserved C-terminal seven-cysteine skeleton 70% homologous to residues 38-139 of SEQ ID NO: 5."

During the interview, the Examiner expressed the concern that TGF-beta may actually fall within the scope of certain generic sequences recited in claim 91, such as Generic Sequence 6 or SEQ ID NO: 31, or Generic Sequence OPX or SEQ ID NO: 29. Since these generic sequences are also recited in the amended claims 97 and 99, Applicants hereby submit additional evidence which demonstrates that none of the three known human TGF-beta molecules fall within the scope of either SEQ ID NO: 29 or SEQ ID NO: 31.

As the instant specification describes on pages 33-39, and 54, SEQ ID NOs: 29 and 31 are defined by the consensus of a number of subject morphogens, such that each "Xaa" in these two generic sequences is specifically defined by a limited subset of the amino acids found in the morphogen sequences used to compile SEQ ID NOs: 29 and 31.

For example, SEQ ID NO: 29 (or "OPX") is based on human OP-1, human OP-2, mouse OP-1, and mouse OP-2. According to page 54, lines 7-12 of the specification, "each Xaa at a given position independently is selected from the residues occurring at the corresponding position in the C-terminal sequence of mouse or human OP1 or OP2 (See Seq. ID Nos. 5-8 and/or Seq. ID Nos. 16-23)." Applicants herewith submit **Exhibit A**, which is a multisequence alignment of the C-terminal 102 amino acids of human OP-1, human OP-2, mouse OP-1, mouse OP-2, and human

TGF-β1, -β2, and β3. Based on this result, it is apparent that none of the TGF-beta molecules can be described by SEQ ID NO: 29, no matter how each Xaa is selected. For example, Xaa at residue 2 of the alignment is either "K" or "R," while all three TGF-beta molecules are "C" at that position. Similar discrepancies can be found at least at residues 3-5, 8, 9, and numerous other positions. Thus, none of the TGF-beta molecules are within the scope of SEQ ID NO: 29.

Similarly, SEQ ID NO: 31 is defined by SEQ ID NOs. 5-14, 16-22, and 24-28 (page 33, last paragraph). According to page 37, lines 30-31, "each Xaa is independently selected from a group of one or more specified amino acids as defined by the following..." Applicants herewith submit **Exhibit B**, which is a multisequence alignment of the C-terminal 102 amino acids of human OP-1, human OP-2, mouse OP-1, mouse OP-2, CBMP-2A (or BMP2), CBMP-2B (or BMP4), DPP, Vg1, Vgr-1, GDF-1, BMP3, BMP-5, BMP-6, and 60A (which are represented by SEQ ID NOs. 5-14, 16-22, and 24-28), and human TGF-β1, -β2, and β3. Based on this result, it is apparent that none of the TGF-beta molecules can be described by SEQ ID NO: 31, no matter how each Xaa is selected. For example, Xaa at residue 2 of the alignment must be one of Lys (K), Arg (R), Ala (A), or Gln (Q) (see **Exhibit B** and page 37, line 33), while all three TGF-beta molecules are "C" at that position. Similar discrepancies can be found at least at residues 3 (V/L in TGF-beta proteins), 16 (K in TGF-beta proteins), 20 (H in TGF-beta proteins), and numerous other positions. Thus, none of the TGF-beta molecules are within the scope of SEQ ID NO: 31.

In summary, none of the three known TGF-beta molecules even come close to being within the scope of clauses (4) and (5) of claims 97 and 99. In addition, there is no other cited molecule that fits the description of SEQ ID NOs: 29 and 31.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: July 23, 2003

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Alignment Report of ExhibitA.meg ClustalV (PAM250)
Tuesday, July 22, 2003 5:16 PM

EXHIBIT A

```
    C C V H E L Y V S F R - D L G W - D W I I A P K G Y A A Y Y C E G E C A F P L S  Majority
                      10                  20                  30                  40
    C K K H E L Y V S F R - D L G W Q D W I I A P E G Y A A Y Y C E G E C A F P L N  hOP-1c
    C K K H E L Y V S F R - D L G W Q D W I I A P E G Y A A Y Y C E G E C A F P L N  mOP-1c
    C R R H E L Y V S F Q - D L G W L D W V I A P Q G Y S A Y Y C E G E C S F P L D  hOP-2c
    C R R H E L Y V S F R - D L G W L D W V I A P Q G Y S A Y Y C E G E C A F P L D  mOP-2c
    C C V R Q L Y I D F R K D L G W - K W I H E P K G Y H A N F C L G P C P Y I W S  hTGF-b1c
    C C L R P L Y I D F K R D L G W - K W I H E P K G Y N A N F C A G A C P Y L W S  hTGF-b2c
    C C V R P L Y I D F R Q D L G W - K W V H E P K G Y Y A N F C S G P C P Y L R S  hTGF-b3c

    S - M N A T N H A I V Q S L V H L I N P D A V P K P C C A P T D L E A L S V L Y  Majority
                      50                  60                  70                  80
40  S Y M N A T N H A I V Q T L V H F I N P E T V P K P C C A P T Q L N A I S V L Y  hOP-1c
40  S Y M N A T N H A I V Q T L V H F I N P D T V P K P C C A P T Q L N A I S V L Y  mOP-1c
40  S C M N A T N H A I L Q S L V H L M M P D A V P K A C C A P T K L S A T S V L Y  hOP-2c
40  S C M N A T N H A I L Q S L V H L M K P D V V P K A C C A P T K L S A T S V L Y  mOP-2c
40  L - - - D T Q Y S K V L A L Y N Q H N P G A S A A P C C V P Q A L E P L P I V Y  hTGF-b1c
40  S - - - D T Q H S R V L S L Y N T I N P E A S A S P C C V S Q D L E P L T I L Y  hTGF-b2c
40  A - - - D T T H S T V L G L Y N T L N P E A S A S P C C V P Q D L E P L T I L Y  hTGF-b3c

    Y D G S S N V I L E K L R N M V V K A C G C H                                    Majority
                      90                  100
80  F D D S S N V I L K K Y R N M V V R A C G C H                                    hOP-1c
80  F D D S S N V I L K K Y R N M V V R A C G C H                                    mOP-1c
80  Y D S S N N V I L R K H R N M V V K A C G C H                                    hOP-2c
80  Y D S S N N V I L R K H R N M V V K A C G C H                                    mOP-2c
77  Y V G R K P K V - E Q L S N M I V R S C K C S                                    hTGF-b1c
77  Y I G K T P K I - E Q L S N M I V K S C K C S                                    hTGF-b2c
77  Y V G R T P K V - E Q L S N M V V K S C K C S                                    hTGF-b3c
```

Decoration 'identity with hOP-1': Box residues that match the Consensus exactly.

Sequence pair distances of ExhibitA.meg ClustalV (PAM250)
Tuesday, July 22, 2003 5:15 PM

Percent Identity

	1	2	3	4	5	6	7	
1		99.0	73.5	75.5	25.5	28.6	27.6	1
2	1.0		74.5	76.5	25.5	27.6	26.5	2
3	32.7	31.2		96.1	21.4	26.5	26.5	3
4	29.7	28.3	4.0		21.4	25.5	26.5	4
5	127.6	127.6	148.3	148.3		74.5	77.6	5
6	114.6	118.8	123.1	127.6	31.2		81.6	6
7	118.8	123.1	123.1	123.1	26.7	21.1		7
	1	2	3	4	5	6	7	

Divergence

1 hOP-1c
2 mOP-1c
3 hOP-2c
4 mOP-2c
5 hTGF-b1c
6 hTGF-b2c
7 hTGF-b3c

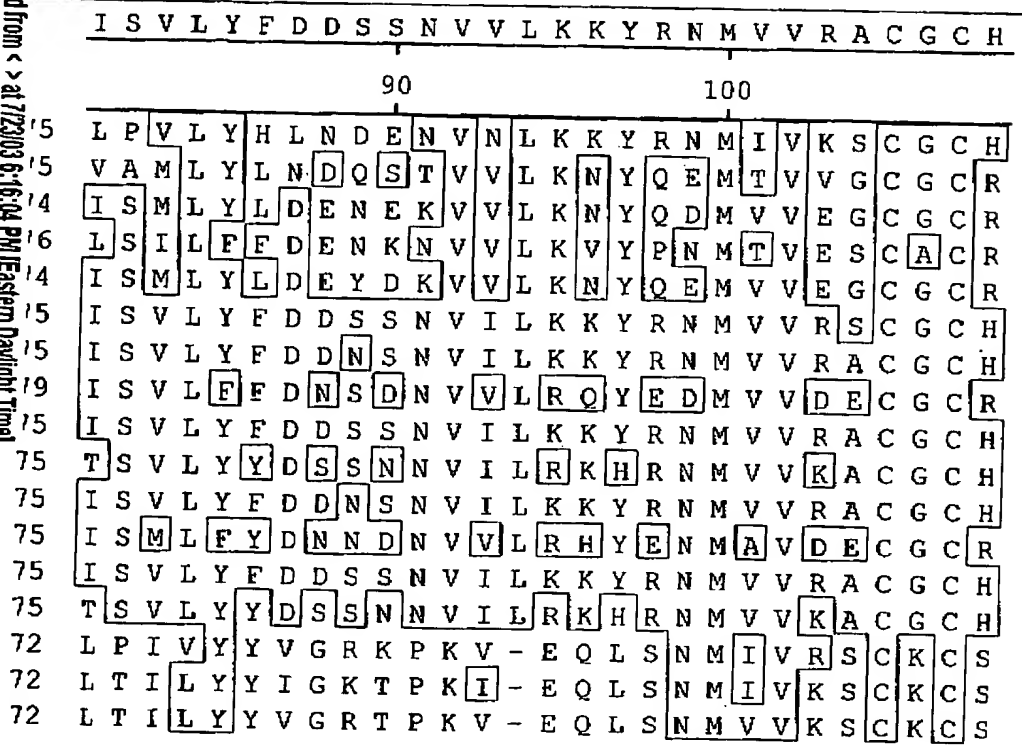
Alignment Report of ExhibitB.meg ClustalV (PAM250)
Tuesday, July 22, 2003 5:58 PM

Page

EXHIBIT B

```
   C K K H E L Y V S F R - D L G W Q D W I I A P K G Y A A N Y C E G E C P F P L N  Majority
                     10                  20                  30                  40
1  C Q M Q T L Y I D F K - D L G W H D W I I A P E G Y G A F Y C S G E C N F P L N  60Ac
1  C R R H S L Y V D F S - D V G W D D W I V A P L G Y D A Y Y C H G K C P F P L A  Dppc
1  C K R H P L Y V D F S - D V G W N D W I V A P P G Y H A F Y C H G E C P F P L A  hBMP2c
1  C A R R Y L K V D F A - D I G W S E W I I S P K S F D A Y Y C S G A C Q F P M P  hBMP3c
1  C R R H S L Y V D F S - D V G W N D W I V A P P G Y Q A F Y C H G D C P F P L A  hBMP4c
1  C K K H E L Y V S F R - D L G W Q D W I I A P E G Y A A F Y C D G E C S F P L N  hBMP5c
1  C R K H E L Y V S F Q - D L G W Q D W I I A P K G Y A A N Y C D G E C S F P L N  hBMP6c
1  C R A R R L Y V S F R - E V G W H R W V I A P R G F L A N Y C Q G Q C A L P V A  hGDF1c
1  C K K H E L Y V S F R - D L G W Q D W I I A P E G Y A A Y Y C E G E C A F P L N  hOP1c
1  C R R H E L Y V S F Q - D L G W L D W V I A P Q G Y S A Y Y C E G E C S F P L D  hOP2c
1  C K K H E L Y V S F Q - D L G W Q D W I I A P K G Y A A N Y C D G E C S F P L N  mBMP6(Vgrl)c
1  C K K R H L Y V E F K - D V G W Q N W V I A P Q G Y M A N Y C Y G E C P Y P L T  xVglc
1  C K K H E L Y V S F R - D L G W Q D W I I A P E G Y A A Y Y C E G E C A F P L N  mOP-1c
1  C R R H E L Y V S F R - D L G W L D W V I A P Q G Y S A Y Y C E G E C A F P L D  mOP-2c
1  C C V R Q L Y I D F R K D L G W K - W I H E P K G Y H A N F C L G P C P Y I W S  hTGF-b1c
1  C C L R P L Y I D F K R D L G W K - W I H E P K G Y N A N F C A G A C P Y L W S  hTGF-b2c
1  C C V R P L Y I D F R Q D L G W K - W V H E P K G Y Y A N F C S G P C P Y L R S  hTGF-b3c
```

```
                A H M N A T - - - - N H A I V Q T L V H L M N P E A - V P K P C C V P T K L S A  Majority
                                    50                  60                  70                  80
  0  A H M N A T - - - - N H A I V Q T L V H L L E P K K - V P K P C C A P T R L G A  60Ac
  0  D H F N S T - - - - N H A V V Q T L V N N M N P G K - V P K A C C V P T Q L D S  Dppc
  0  D H L N S T - - - - N H A I V Q T L V N S V N S - K - I P K A C C V P T E L S A  hBMP2c
  0  K S L K P S - - - - N H A T I Q S I V R A V G V V P G I P E P C C V P E K M S S  hBMP3c
  0  D H L N S T - - - - N H A I V Q T L V N S V N S - S - I P K A C C V P T E L S A  hBMP4c
  0  A H M N A T - - - - N H A I V Q T L V H L M F P D H - V P K P C C A P T K L N A  hBMP5c
  0  A H M N A T - - - - N H A I V Q T L V H L M N P E Y - V P K P C C A P T K L N A  hBMP6c
  0  L S G S G G P P A L N H A V L R A L M H A A A P G A - A D L P C C V P A R L S P  hGDF1c
  0  S Y M N A T - - - - N H A I V Q T L V H F I N P E T - V P K P C C A P T Q L N A  hOP1c
 40  S C M N A T - - - - N H A I L Q S L V H L M K P N A - V P K A C C A P T K L S A  hOP2c
 40  A H M N A T - - - - N H A I V Q T L V H L M N P E Y - V P K P C C A P T K L N A  mBMP6(Vgr1)c
 40  E I L N G S - - - - N H A I L Q T L V H S I E P E D - I P L P C C V P T K M S P  xVg1c
 40  S Y M N A T - - - - N H A I V Q T L V H F I N P D T - V P K P C C A P T Q L N A  mOP-1c
 40  S C M N A T - - - - N H A I L Q S L V H L M K P D V - V P K A C C A P T K L S A  mOP-2c
 40  L D T Q - - - - - - - - Y S K V L A L Y N Q H N P G A S - A A P C C V P Q A L E P  hTGF-b1c
 40  S D T Q - - - - - - - - H S R V L S L Y N T I N P E A S - A S P C C V S Q D L E P  hTGF-b2c
 40  A D T T - - - - - - - - H S T V L G L Y N T L N P E A S - A S P C C V P Q D L E P  hTGF-b3c
```



Decoration 'Identity to hOP-1': Box residues that match hOP1c exactly.